Guidance document on the content of the rapporteur's day 80 critical assessment report for generic medicinal products (Article 10.1 only)

Quality aspects

<(Invented) Name>

<(Active Substance)>

EMEA/H/C/<xxx>

Applicant:

CHMP Rapporteur:	
EMA EPL:	
EMA PM:	
Start of the procedure:	
Date of this report:	
Deadline for comments:	

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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ADMINISTRATIVE INFORMATION

<Invented> name of the generic medicinal product:	
INN (or common name) of the active substance(s):	
Active substance(s):	
Applicant:	
Applied Indication(s):	
Pharmaco-therapeutic group (ATC Code):	
Pharmaceutical form(s) and strength(s):	
Rapporteur contact person: **EMA Product Team Leader:**	**Name:** Tel: Fax: Email:
Names of the Rapporteur assessors (internal and external):	**Quality:** **Name(s)** Tel: Fax: Email: **Non-clinical:** **Name(s)** Tel: Fax: Email: **Clinical :** **Name(s)** Tel: Fax: Email:

Declarations

☐ The assessor confirms that proprietary information on, or reference to, third parties (e.g. ASMF holder) or products are not included in this assessment, unless there are previous contracts and/or agreements with the third party(ies).

☐ The assessor confirms that reference to ongoing assessments or development plans for other products is not included in this assessment report.

Whenever the above box is un-ticked please indicate section and page where confidential information is located here:

LIST OF ABBREVIATIONS

QUALITY CRITICAL ASSESSMENT

The following structure for the quality assessment report of a generic product keeps basically to the CTD structure of the dossier, apart from some preliminary sections, e.g. an Introduction section to put the product in context.

Certain Modules in a generic dossier may be abridged (e.g. Modules 4 & 5) but this option does not apply to the Quality Module 3 which must be complete. The norm is that a generic product should be assessed primarily on its own merits, i.e. as a stand-alone dossier.

The legislation does not require the generic product to be identical to the reference product. While the active substances must be the same with regard to qualitative and quantitative aspects , certain differences may exist particularly with regard to composition of the product (excipients), impurity profiles, etc. It is useful to record such observed differences for information. However, some assessors reserve the right to obtain additional relevant quality information from the dossier of the authorised reference product where necessary, in order to satisfy themselves on matters of concern.

Please also refer to the CTD guidance text for the applicant – it is not considered necessary to repeat this here, but rather to highlight some additional aspects not specifically detailed in the CTD, for the benefit of assessors. Note that for simplicity, not all CTD headings are reproduced in the report structure that follows, only the 'main' headings. Assessors may add more, or less, depending upon the complexity of the product. In addition, note also that the CTD terms 'Drug Substance' and 'Drug Product' are synonymous with the EU legislative terms 'Active Substance' and 'Finished Product' respectively.

Reference to information, which is confidential and should not be seen by the applicant (e.g. reference to the assessment of another medicinal product) should be clearly marked as "Confidential" and highlighted using a yellow background. These sections will be removed before the assessment is sent to the applicant.

Like the Rapporteurs' report for an NCE product, this quality assessment report for a generic should be 'self-standing'. This may be achieved in two ways:

1) Presenting or copying data which are taken from the applicant's dossier, followed by the assessor's own critical assessment of these data, particularly with respect to safety/efficacy consequences and highlighting adherence to specific guidance documents. The heading

'Assessor's Comments' should be introduced as a separator in this case, to avoid confusion

2) Alternatively, this report may consist largely of the assessor's own views with references to the applicant's own data and/or Quality Overall Summary (QOS). In this case, the assessor's views are intended to be read in conjunction with the QOS which must be attached. The additional headings for assessor's comments would not be needed. See specific CHMP or CHMP/ICH Notes for guidance as a general framework for quality assessment, e.g.: The Rules Governing Medicinal Products in the EU, volume 3A http://www.emea.eu.int/index/indexh1.htm: The Notice to Applicants revision incorporating the CTD.*

In addition, other multidisciplinary guidelines not indexed under 'quality' may also be relevant, and certain 'technical' legislation may also be relevant, e.g. Directive 89/343/EEC relating to radiopharmaceuticals. In general, assessors should try to relate quality matters to efficacy and safety consequences as much as possible. Matters arising from the scientific evaluation below, which have a bearing on the product information, should also be mentioned (comments on the SPC, Labels & Package Leaflet.). Assessors are encouraged to complete the proforma for sampling and testing attached to the end of this template (Annex 2) to assist in the post-authorisation sampling and testing scheme for Centrally-authorised products coordinated by the EMEA Inspections function.

** a limited amount of the applicant's data such as flow diagrams, specifications etc. may be copied in, to facilitate the reading of the report.*

1. REQUESTS FOR INSPECTION ACTION PRIOR TO AUTHORISATION:

Where a site has already been inspected, such requests are expected to be uncommon. However, when quality issues requiring a future inspection are identified during the dossier assessment phase, they should be notified as soon as possible to the relevant Inspections authority.

Because on-site Inspection takes time to organise, it is not necessary to wait until day 80 if the assessor considers such action is necessary prior to authorisation. The relevant Inspection

authority (e.g. EMEA in the case of centrally-authorised products) should be notified; if possible, in advance of the day 80 assessment report and this request should be highlighted in this part of the assessment report at day 80.

It is important to note that such requests may be made to resolve questions in any part of the quality dossier, and the reasons for the request should be briefly described here and in more detail in the relevant section of the report which follows, e.g. S.2, P.3, etc, for either GMP-compliance and/or product-process specific inspections.

• Active substance manufacturing site:

Since 30 October 2005, the Directive 2004/27/EC introduces a equirement for manufacturing authorisation holders to use only active substances which have been manufactured according to GMP in the manufacture of medicinal products. The GMP Basic Requirements for Active Substances used as Starting Materials have been introduced as a Part II to the GMP guide. It is the responsibility of the manufacturing authorisation holders using the active substance as a starting material to ensure the GMP compliance of their suppliers of active substances. However, inspections by EU GMP inspectors may be requested on when there are causes for concern raised during the assessment for any site. Ad hoc GMP Inspection Services has adopted a guidance on the occasions when it is appropriate for Competent Authorities to conduct inspections

at the premises of Manufacturers of Active Substances used as starting materials and this document is incorporated into the Compilation of Community Procedures and can be found at

http://www.emea.europa.eu/Inspections/GMPCompproc. It should be

particularly noted that inspections should be triggered automatically in the case of the sterilisation step of a sterile active substance when there is no evidence that the site in question is subject to routine inspection by a National Competent Authority of the EEA (in some Member States a manufacturing authorisation is required for these activities and in these cases the guidance given below for finished product manufacturing sites applies).

• Finished product manufacturing site

This includes all stages of manufacture of the medicinal product including intermediate stages and quality control. For sites located in the EEA, importation and batch release (certification) are also included):

- Site located in the EEA:

The Supervisory Authority of the Member State on a routine basis

inspects this site for GMP. An inspection is requested only if there are specific issues connected with assessment of the application.

- Site outside the EEA:

** GMP:*

An inspection of the site is not requested, unless product or process related issues arise in the assessment (see below), if a valid GMP certificate (or entry in EudraGMDP database) issued by an EEA or MRA product is available for the same category of product. The validity date does not mean that the certificate is expired. The issuing authority will confirm the validity.

** Product/process:*

An inspection may always be requested to cover product or process specific issues. In which case, a list of questions/items should be provided to the inspectorate, which should be addressed during the

inspection. If you are recommending an inspection, please also consider any recommendations for the composition of the inspection team.

A question should be raised to the applicant in order to be able to conduct the inspection during the clock stop.

TESTING:

If testing is recommended for applications under the centralised procedure, please define the testing protocol (type of samples: active, bulk, finished product / tests to be carried out / number of samples /number of batches / Official testing laboratory) and summarise the results for the Committee as soon as possible. If assistance is needed to identify a relevant laboratory, please contact EMA (Manufacturing and Quality Compliance Service) who can provide assistance within the framework of the EMA sampling and testing programme.

2. INTRODUCTION

General background of the product.
Brief description of the product type (active substance, pharmaceutical form, container, radiopharmaceutical, herbal, etc.) Indications, target population, posology (with regard to the ability of the product to deliver this posology, e.g. scored tablets), method of administration (if unusual, e.g. using a device).The information provided here is intended to provide a brief description

of the main features of the product. The amount of information provided will depend on the nature of the particular product. The clinical context of use should also be briefly mentioned.

3. DRUG SUBSTANCE

- It should be mentioned whether a CEP or ASMF procedure or full information in the dossier of the AS in the dossier is used.
In case the ASMF procedure is used it should be mentioned that the assessment of the Active Substance Master File (ASMF) is provided in a separate ASMF Assessment Report with a confidential annex on the Restricted Part.

- Where there is more than one ASMF cited in the dossier, a separate report is provided for each ASMF

- Letters of Access in relation to specific drug products should be described for the product in question.

- When a CEP or ASMF is used, only section III.4 Control of Drug Substance and III.5 Reference Standards or Materials relating to the product manufacturer need completing, unless the applicant has provided additional data e.g. 3.2.S.7 stability data to support a longer re-test period

- The questions to the restricted part of the ASMF reports will not be sent to the MAH but only to the relevant ASM/holder of the ASMF

- Where ASMF or CEP is applicable, clarify the source (applicant or ASMF holder or CEP holder) and level of details to be drafted in the assessment report.

- The assessment of the drug substance in this AR should only address additional information provided by the applicant, which is not included in the open part as provided by the ASMF holder. In case a full dossier for the Active Substance is provided by the applicant the full assessment of the active substance should be included in the day 80 AR.

3.1. General information (CTD module 3.2.S.1)

S.1.1 Nomenclature (CTD section: S.1.1)

At least one sentence to mention the name. Confirm whether the name is rINN, or Common Name, etc. State the IUPAC Chemical name, CAS registry etc.

International non-proprietary name (INN):	
United States Adopted Name (USAN):	
Chemical names:	
Other name:	
CAS registry number:	
Laboratory code:	
Molecular formula:	
Relative molecular mass:	

Structural formula (CTD section: S.1.2):

Include and link to similar compounds, by description or by structure.

General properties (CTD section: S.1.3)

Physical characteristics:	
Solubility:	
pK_a-value:	
Partition coefficient:	
Hygroscopicity:	
Stereochemistry:	
Polymorphism	

Indicate crucial properties and give values, e.g., pKa, solubility, etc. where relevant.

• State if there is a PhEur monograph for the active substance(s)
• State the source of the information on the active substance, e.g. CEP or AS Master File
• Mention if the active substance is present as a different salt, ester, complex, etc. than the active substance in the reference product.

Assessor's comments on S.1 General Information

Manufacturer(s) (CTD section: S.2.1)

In general, critical statements are needed on the adequacy of the description of the synthesis, of the control of the materials and intermediates, reproducibility of the manufacturing process identifying those issues not adequately covered and which need to be addressed in the LoQ (with reference to number if wanted). Identify 'Major' issues Manufacturer(s) (CTD section: S.2.1)

GMP

Description of manufacturing process and process controls (CTD section:S.2.2)

• Description of manufacturing process and process controls: Flow diagram (incorporate it if possible, rather than present in an Annex) with indication of the critical steps.

• Alternate processes – if mentioned, include comment.

• Reprocessing – if mentioned, include comment (e.g., when could this occur).

• Catalysts and solvents - include comment if not in the main application (but in ASM Restricted part of an ASMF).

Control of materials (CTD section: S.2.3)

State adequacy/extent of proposed specifications for intermediates, reagents, etc.

Control of critical steps and intermediates (CTD section: S.2.4)

Indicate the adequacy of process control.

Process validation and/or evaluation (CTD section: S.2.5)

Brief summary of the extent of data and results.

Manufacturing process development (CTD section: S.2.6)

Brief summary of the extent of data and results with reference to substance used preclinical/clinical studies if applicable.

Assessor's comments on S.2 Manufacture:

3.2. Characterisation (CTD module 3.2.S.3)

The generic dossier should be regarded as a 'stand-alone' dossier, and is assessed on its own merits like any other dossier:

- Application of ICH / PhEur principles

- Below threshold – OK, no problem

- Above thresholds – Identification. Qualification, either by tox. studies or by other means in the current ICH guideline

- Concerning qualification, the generic applicant must provide this justification in their dossier and this should be summarised in the report

- comparative data between generic and reference products for impurities above the qualification threshold may be available in some cases, and are of course useful in the context of "qualification by use", but these comparative data should be provided by the generic applicant in their dossier. The assessor does not normally look into the dossier of the reference product in order to look for supplementary information which is not present in the generic dossier. In this regard, the generic applicant has to submit a comprehensive dossier demonstrating the suitability of the product for its intended purpose. It is not the assessor's responsibility to justify the suitability of the product, but to assess if the information provided by the applicant is adequate.

• Conclusion on the adequacy of the company's approach to the control and qualification of impurities, with particular reference to non- clinical (toxicology) studies (and clinical studies where relevant).

• For radiopharmaceuticals, mention also radiochemical purity and radionuclidic purity.

Elucidation of structure and other characteristics (CTD section: S.3.1)

• Elucidation of structure and other characteristics: Summary of methods used to elucidate the structure and characterise properties of the active substance, e.g., chirality, polymorphism, etc.

• In the case of radiopharmaceuticals, it should be made clear what the active substance is considered to be, i.e. unlabelled ligand, radiolabelled substance, or radiolabel for labelling of another 'carrier' molecule. (In this latter case information is normally included in the 'carrier'dossier).

• In general, critical statements are especially needed on the issue of whether or not methods used for elucidation of structure are adequate.

Impurities (CTD section: S.3.2)

• Impurities: emphasise process-related impurities, solvents, reagents, etc here. Maybe use text in QOS for summary tables of these data. (degradation products may be discussed under stability data S.4.)

• Qualification of generic impurities:

Normally, the existence of a CEP or compliance with a PhEur monograph would generally be taken as indicating the satisfactory quality of the active substance. In the absence of a PhEur monograph, ICH principles should be applied.

Assessor's comments on S.3 Characterisation:

3.3. Control of drug substance (CTD module 3.2.S.4)

Specification (CTD section: S.4.1)

Table of specification to be inserted. Concerning impurity levels in the specification see also the notes under III.3 (Impurities S.3.2)

Table S. 4-1. Specifications

Specification parameter	Test method	Test limits

Specification parameter	Test method	Test limits

Analytical procedure (CTD section: S.4.2)

Combine in above table – just refer to method.

Validation of analytical procedure (CTD section: S.4.3)

State if in accordance with ICH or not, and mention any deviation.

• Are the methods adequate to control the substance on a routine basis?

Table S.4-2. Summary of Validation of Analytical Procedures

Analytical procedure

	Analytical procedure			
Accuracy				
Precision: - Repeatability - Intermediate precision				
Specificity				
Detection limit				
Quantitation limit				
Linearity				
Range				
Robustness				
Solution stability				

+ indicates that the parameter is acceptably tested

- indicates that the parameter is not tested

? indicates that questions remains before the parameter is judged to be acceptable

Batch analyses (CTD section: S.4.4)

• Batch analysis results (n=?); do these confirm consistency & uniformity of the product? Do they indicate that the process is under control?

Justification of specification (CTD section: S .4.5)

• Is the applicant's proposed justification of the specification adequate or not, bearing in mind the intended use of the drug substance in the product.

Assessor's comments on S.4 Control of Drug Substance:

3.4. Reference standards of materials (CTD module 3.2.S.5)

Assessor's comments on S.5 Reference Standards or Materials:

3.5. Container closure system (CTD module 3.2.S.6)

• Is the choice of the container/closure justified, bearing in mind the physical/chemicalproperties of the drug substance?

• Does it provide adequate protection from microbial contamination, if this is considered to be necessary?

• Confirm that the containers proposed for routine storage are those which have been used in the stability studies supporting the re-test period (ref. S.7).

Assessor's comments on S.6 Container Closure System:

3.6. Stability (CTD module 3.2.S.7)

Stability summary and conclusion (CTD section: S.7.1)

• State if the studies are carried out in accordance with current ICH/CHMP guidelines. Are there deviations? Are the deviations justified in this case?

• Stability summary and conclusions: Reference to any differences in manufacturing. Processes used, with comments on whether or not this has a significant effect on the stability profile.

• Discuss the relevance of the protocol, particularly with regard to the parameters tested in the studies.

• Confirm that the analytical methods are stability-indicating (ref. S.4). Stability indicating tests should be chosen, which are able to detect significant changes in the quality of the product.

• Confirm that the containers used in the stability studies are the same as those proposed for routine storage (ref. S.6).

• Final conclusion on whether or not the proposed re-test period is justified.

Table S. 7-1. Stability studies

Temp °C, RH %	n batches x months	Batch size	Package
25 °C / 60% RH		Production scale / Pilot scale	Intended for marketing
40 °C / 75% RH			

Post-approval stability protocol and stability commitments (CTD section: S.7.2)

Stability data (CTD section: S.7.3)

The stability data on which the summary and conclusion in S.7.1 is based, is included in the dossier.

Assessor's comments on S.7 Stability:

4. Drug product (CTD module 3.2.P)

4.1. Description and composition of the drug product (CTD module 3.2.P.1)

Don't forget to cite all components of the presentation as intended for marketing, including reconstitution diluents, medical devices, etc.

• The qualitative composition of a generic may be different to the reference product, and the assessor should mention the observed

differences for information, assuming they are justified in the generic dossier in the normal way, i.e. with reference to bioequivalence, stability etc.

• In particular where the product presentation includes a medical device, it is important to cross-refer to the details of the device in 3.2R, Regional Information. Check that any medical devices are CE-marked prior to submission of the dossier for the medicinal product.

• Whilst the composition may be obvious, it may be necessary to pay particular attention to the details of the container/closure system, especially for labile or sterile products. The composition of {drug product} is presented in Table P.1-1 below.

Table P. 1-1. Complete composition of XXX

Ingredient	Reference	XXX Amount (XXX)	XXX Amount (XXX)	Function
				Active

Assessor's comments on P.1 Description and Composition of the Drug Product:

4.2. Pharmaceutical development (CTD module 3.2.P.2)

The pharmaceutical development of a generic product should be described and justified according to current EU guidelines.

Components of the drug product (CTD section:P.2.1)

Drug substance (CTD section: P.2.1.1)

Has the company identified those physico-chemical properties of the drug substance that are of relevance for product performance?

• Have these properties been adequately specified?

• On what basis have the limits been justified?

• Where potentially key parameters are not controlled, is the justification for their omission acceptable?

• Use of materials of animal or human origin – have these been justified?

Excipients (CTD section: P.2.1.2)

• Have important, novel or unusual excipients been identified regarding their impact on product performance?

• The applicant's choice and function of key excipients should be mentioned, e.g. those modifying release or disposition of the drug substance. In some cases (e.g. gas dispersions for diagnostic ultrasound investigations) the total formulation or system is responsible for the clinical efficacy of the product and these cases should be discussed in detail.

• Assessors should also refer to section V of this report (CTD Appendix 3.2.A.3, Novel Excipients), where a more detailed evaluation of the excipient per se may be given. Note that

'new' excipients not present in products authorised in the EU may be regarded as new active substances and data requirements are 'full', i.e. manufacture and control, reference to toxicology studies, etc.

Drug product (CTD section: P.2.2)

• Formulation Development: is the formulation development based on sound scientific principles? Discussion of the development of the dissolution test method, description of changes, demonstration of discriminatory properties. Results of studies to establish IVIVC if relevant.

Formulation development (CTD section: P.2.2.1)

Has the applicant presented the Target Product Profile of the product, i.e. the quality characteristics that the product should have to ensure the desired quality taking into account safety and efficacy? Is the formulation developmentsupported by clinical development? Discussion of bioequivalence between commercial formulation and clinical trial formulations, if different. Discuss if possible differences in finished product quality attributes (e.g. impurity and dissolution profile). Discussion of the development of the dissolution test method, description of changes, demonstration of discriminatory properties. Results of studies to establish IVIVC, if relevant.

Early development formulations for pre-clinical and clinical studies should be highlighted where relevant, and comments made relating to the findings of these studies. Additional details should be given if the development encompasses a paediatric formulation including information for which age group this isintended, if appropriate.

Bioequivalence study and reference product / Clinical formulation

Overages (CTD section: P.2.2.2)

• Overages: On which basis are overages justified?

Physico-chemical and Biological properties:• Are key parameters identified and adequately controlled?

The CTD-Q gives an adequate list of parameters that need to be discussed with regard to their impact on the performance of the product, where relevant. e.g. for tablets – the particle size and polymorphism of an active substance with low aqueous solubility may need to be discussed with reference to their effects on dissolution and bioavailability. In this example the pH-solubility profile would also be relevant basic information having an impact on the choice of dissolution test methodology.

Physicochemical and biological properties (CTD section: P.2.2.3)

Manufacturing process development (CTD section: P.2.3)

Manufacturing Process Development:

• If the manufacturing process of the product influences the physicochemical properties of the drug substance (e.g. polymorphic form), check that the studies carried out on the drug substance remain valid.

• Has the choice of process been justified, where necessary? Are critical process parameters, relevant for subsequent process validation, identified? Are differences in the manufacturing processes of the commercial product and clinical trial material adequately explained and discussed?

Container closure system (CTD section: P.2.4)

• Is the choice of materials for the container and closure adequate to support the stability and use of the product?

• Technical properties of the container closure system with respect to patient use should be considered, e.g. nasal sprays, inhalers, prefilled syringes.

Microbiological attributes (CTD section: P.2.5)

• Microbiological Attributes: Is the use of additives, e.g. preservatives and antioxidants justified regarding their concentration and nature?

Compatibility (CTD section: P.2.6)

• Do the compatibility studies support the instructions for use and handling in the SPC?

Assessor's comments on P.2 Pharmaceutical Development:

4.3. Manufacture (CTD module 3.2.P.3)

• The assessor should discuss any specialised processes that may need to be inspected (see preamble to this report).
• Confirm that process holding times and transport arrangements are relevant and have been justified.
• Any requests for 'parametric release' need to be fully evaluated and commented on here, with a comment from the GMP Inspectors, where necessary, in accordance with the CPMP NfG.
• Where relevant, the safety of the product in respect of transmission of 'adventitious agents' should be considered under Appendix A.2 (Note: This is perhaps more relevant for biotech/biological products, outside the scope of this template).

Manufacturer(s) (CTD section: P.3.1)

• The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in the manufacturing and testing should be provided.
• Description of manufacturing process and process controls: Flow diagram (incorporate it if possible, rather

than present in an Annex) with indication of the critical steps.
• Where the product consists of the active substance without excipients details of the manufacturers should also be referred to here and should be accordingly licensed.

Batch formula (CTD section: P.3.2)

• Where ranges of batch size are proposed for production, blending of batches or the use of sub batches, the acceptability should be addressed.

Description of manufacturing process and process controls (CTD section: P.3.3)

Controls of critical steps and intermediates (CTD section: P.3.4)

Process validation and/or evaluation (CTD section: P.3.5)

• The assessor should comment here on whether process validation data are needed in the dossier (i.e. whether it is needed prior to authorisation). Where non-standard methods are used these validation data would normally be expected. For standard processes the process validation scheme referred to in 3.2.R Regional Information should be evaluated.

Assessor's comments on P.3 Manufacture:

4.4. Control of excipients (CTD module 3.2.P.4)

• If PhEur monograph exists, mention may be brief and should be enough in most cases.

• If non-PhEur, is the specification adequate?

• Do the specifications and tests reflect the functionality in a relevant way? Especially in novel delivery systems, some ingredients may have a special function, and should be described and controlled in more detail, especially with regard to functionality testing.

• Note that 'new' excipients not present in products authorised in the EU may be treated as new active substances and data requirements are

'full', i.e. manufacture and control, reference to toxicology studies, etc. (Detailed assessment of these special new excipients should be discussed under section V of this report, CTD-Q Appendix A3 below)

Specifications (CTD section: P.4.1)

Analytical procedures (CTD section: P.4.2)

Validation of analytical procedures (CTD section: P.4.3)

Justifications of specifications (CTD section: P.4.4)

Excipients of human and animal origin (CTD section: P.4.5)

Novel excipients (CTD section: P.4.6)

Assessor's comments on P.4 Control of Excipients:

4.5. Control of drug product (CTD module 3.2.P.5)

• For radiopharmaceuticals, a discussion of radiochemical purity of reconstituted 'cold' kits should be discussed, where relevant.

Specification(s) (CTD section: P.5.1)

• Specification: Release and shelf life specifications should be presented side by side in tabular form, with brief reference to the method used.Specification summary, important tests, particularly relating to bioavailability/efficacy (e.g. dissolution, particle size, polymorphism if relevant.) and safety (impurities or sterility, pyrogens etc. for sterile products). The general relevance of the release specification should be discussed considering the method of manufacture and clinical use, route of administration etc.

Table P. 5-1. Release and shelf-life specifications

Specification parameter	Test method	Test limits

Specification parameter	Test method	Test limits

Analytical procedures (CTD section: P.5.2)

Validation of analytical procedures (CTD section: P.5.3)

• Validation of analytical procedures: State if in accordance with ICH or not, and mention any deviations. (All control methods, regardless of whether they are applicable to control at release or to the shelf life should be discussed here, under P.5).

Table P. 5-2. Summary of validation of analytical procedures

Analytical procedure

	Analytical procedure			
Accuracy				
Precision - Repeatability - Intermediate precision				
Specificity				
Detection limit				
Quantitation limit				
Linearity				
Range				
Robustness				
Solution stability				

+ indicates that the parameter is acceptably tested

- indicates that the parameter is not tested

? indicates that questions remains before the parameter is judged to be acceptable

Batch analyses (CTD section: P.5.4)

• Batch analysis results (n=?); do these confirm consistency & uniformity of the product? Do they indicate that the process is under control?

Characterisation of impurities (CTD section: P.5.5)

• Note that the tests for impurities in the product specification should focus on degradation products arising from the manufacturing process and those expected during storage, rather than manufacturing process-related impurities carried over in the drug substance if these are controlled in the drug substance and do not change in the product during storage.

• impurities/degradants in generic products:

See the comments under III.3 of this report (CTD S.3.2 impurities in the active substance).

The same principles apply here in relation to impurities/degradants in the product.

Justification of specification(s) (CTD section: P.5.6)

Assessor's comments on P.5 Control of Drug Product:

4.6. Reference standards or materials (CTD module 3.2.P.6)

Assessor's comments on P.6 Reference Standards or Materials:

4.7. Container closure system (CTD module 3.2.P.7)

• State if the studies are carried out in accordance with current ICH/CHMP guidelines. Are there deviations? Are the deviations justified in this case?

• Discuss the relevance of the protocol, particularly with regard to the parameters tested in the studies.

Bracketing & Matrixing designs – acceptable?

• Are the methods used the same as or different to those described in P.5? Are they well validated and shown to be stability indicating?

• Confirm that the containers used in the stability studies are the same as those proposed for routine storage.

• Note that the qualification of impurities carried out on the active substance may not necessarily address degradants induced by the product matrix or product manufacturing process, and this may

need to be addressed with reference to other nonclinical studies if necessary. In addition, apart from degradation products, other product characteristics may change on storage.

In-Use stability:

• Comment also on stability after opening and during use, e.g. for infusions to be diluted, stability after dilution and during administration, compatibility with commercially available administration equipment, etc. Are an in-use shelf life and storage conditions necessary? Are the applicant's proposals in line with the current guidelines? If not, are they still justified?

• For radiopharmaceuticals, a discussion of user-reconstitution methods for 'cold' kits may be discussed here, together with a discussion of post-reconstitution stability.

General:

• Are all of the above considerations correctly reflected in the SPC/package leaflet? Assessor should make a conclusion on whether or not all shelf lives and storage conditions defined inthe SPC are justified.

Assessor's comments on P.7 Container Closure System:

4.8. Stability (CTD module 3.2.P.8)

Stability summary and conclusion (CTD section: P.8.1)

Temp °C, RH %	n batches x months	Batch size	Package
25 °C / 60% RH		Production scale / Pilot scale	Intended for marketing
40 °C / 75% RH			

Post-approval stability protocol and stability commitment (CTD section: P.8.2)

Stability data (CTD section: P.8.3)

The stability data on which the summary and conclusion in P.8.1 is based, is included in the dossier.

Assessor's comments on P.8 Stability:

5. Appendices (CTD module 3.2.A)

Facilities and equipment

Adventitious agents safety evaluation

(When relevant for chemical generics)

Novel excipients

Note that 'new' excipients not present in products authorised in the EU may be regarded as new active substances and data requirements are 'full', i.e. manufacture and control, reference to toxicology studies, etc. (Detailed assessment of these special new excipients should be discussed here)

6. Regional information

Process validation scheme for the drug product

Medical device issues

TSE Issues

7. Assessor's comments on the SmPC, labels and package leaflet

8. Assessor's overall conclusions on quality

Brief summary of the main conclusions

9. List of questions as proposed by the rapporteur

Also, state whether or not there is a need for a GMP inspection. Where an inspection has already been requested this should be stated.

Quality aspects

Major objections

Drug substance **[related to additional data provided by applicant only]**

Drug substance **[applicant's part as provided by ASMF holder]**

Note: In case the ASMF procedure is used the following should be stated in case potential serious risks to public health are being raised on the restricted part of the ASMF:

<For potential serious risks to public health on the restricted part of the ASMF see separate AR on the ASMF>

Drug product

Other concerns

Drug substance **[related to additional data provided by applicant only]**

Note: When applicable: <For Other concerns on the restricted part of the ASMF see separate AR on the ASMF>

Drug product

10. ANNEX 1 (as appropriate)

Active Substance Master File (ASMF) Assessment Report(s) – in separate document(s).

11. ANNEX 2 (For centrally – submitted product)

Proposals for post-authorisation Sampling and Testing

Doc. Ref: EMEA/INS/3924/02 Proposals from the Rapporteur / Co-Rapporteur[1] on "Essential Quality Parameters to be tested for the Control of Marketed Centrally Authorised Product"

NAME OF MEDICINAL PRODUCT -	Application number: EMEA/ / / Authorisation number: EU/ /
Active substance -	☐ NCE ☐ Other

Active substance **(please see guidance given above)**	Rationale for testing[2] *(specification and test method, when appropriate)*
☐ No control	.....
☐ Identity	.....
☐ Assay / activity	.....
☐ Purity (Main impurities - Manufacturing)	.....
☐ Other parameters	.....

Following a critical review the following quality test parameters have been selected for testing by OMCLs during post-authorisation surveillance

Medicinal Product	**Comments** *(specification and test method, if several methods are possible for a parameter please specify which method(s) should be applied)*
☐ No control	
☐ Identity	.....
☐ Assay / activity	.....
☐ Purity (main impurities - stability)	.....
☐ Dissolution	.....
☐ Uniformity of dosage units	.....
☐ Moisture Content	.....
☐ Other parameters	.....

Recommendation, when applicable, on pharmaceutical form / strength / presentation to be tested

Please record below the name, organisation and telephone number of a contact person

Name: _____

Organisation: _____

Telephone Nr.: _____

[1] Delete as appropriate
[2] A (short) rationale should be provided for each test selected for the active substance.

Assessor-identified weighting factors to be taken into account in the risk-based selection of products for testing

☐ An inherent variability in the production process

☐ Inherent difficulties foreseen with the testing methodology

☐ Novel manufacturing or control technology[3]

☐ Potential presence of toxic impurities

☐ A particular risk of bioavailability problems

☐ A particular risk inherent in the manufacturing or control methodology not covered by any of the above (explanatory comments may be made below).

.....

.....

☐ None of the above weighting factors apply

[3] Note: PAT or new ICH approaches to quality are expected to lead to enhanced product and process knowledge and improved quality assurance rather than increased risk but it is accepted that assessors may wish to express caution in some cases until there is greater experience and confidence.